INHIBITION OF O-GLCNACASE MITIGATES MOTOR AND BREATHING DEFECTS AND PROLONGS SURVIVAL OF TAU-P301L MICE

P. Borghgraef¹, C. Menuet², H. Devijver¹, L. Gielis¹, H. Gijsen³, D. Moechars³, G. Hilaire², F. Van Leuven¹

¹Experimental Genetics Group - LEGTEGG, KULeuven, Leuven, Belgium, ²MP3-Respiration - UMR CNRS 6231, Faculté St Jerome, Marseille, France, ³Janssen-R&D, Janssen Pharma, Beerse, Belgium

Introduction & aim: Define in vivo the effect of chronic inhibition of O-GlcNAcase on clinical and pathological parameters of Tau-P301L mice (Terwel et al, 2005; Dutschmann et al, 2010).

Methods: Mice were treated daily with O-GlcNAcase inhibitor for 2.5 months and analyzed for body-weight, clasping, rotarod, plethysmography, mortality, brain biochemistry and immuno-histochemistry.

Results: Treatment with O-GlcNAcase inhibitor increased O-GlcNAcylated proteins rapidly and stably, while pT231.Tau was increased and pS21.GSK3α significantly decreased. Double chamber plethysmography demonstrated significant improvement of nasal/chest ratio breathing parameters of Tau-P301L mice (age 6 and 8 months) already after 3 days of oral treatment with O-GlcNAcase inhibitor. Chronic treatment of Tau-P301L mice (from age 7 to 9.5 months) mitigated significantly the loss in body-weight and the motor deficits (clasping, rotarod performance) as opposed to progressive worsening of all parameters in placebo treated, age-matched Tau-P301L mice. Most markedly, nearly 60% of O-GlcNAcase inhibitor treated mice survived at the fixed endpoint of the treatment (age 9.5 months) in contrast to only 10% of the placebo treated Tau-P301L mice.

Conclusion: Our studies establish that inhibition of O-GlcNAcase prolongs the survival, rescues or delays the motor impairment and mitigates the brainstem breathing defect of ageing Tau-P301L mice.
